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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/446,820	04/30/2001	Joseph G Sodroski	157/48436	2949

7590 07/15/2003

Ronald I Eisenstein
Nixon Peabody
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Boston, MA 02110

EXAMINER	
PARKIN, JEFFREY S	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

RIEINV

Office Action Summary	Application No. 09/446,820	Applicant(s) SODROSKI ET AL.
	Examiner Jeffrey S. Parkin, Ph.D.	Art Unit 1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Office Action

Status of the Claims

1. Claims 1-16 are pending in the instant application.

35 U.S.C. § 120

2. If applicant desires priority under 35 U.S.C. § 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of non-provisional application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application. If applicant desires priority based upon a National Stage filing, this information should also be referenced in the first sentence of the specification (i.e., This application is a National Stage entry of International Application No. PCT/CCPY/NNNNN, filed , 199N). Applicants are also required to set forth the relationship between the applications (e.g., continuation, divisional, continuation-in-part) upon which priority is desired. It is noted that applicants are claiming priority to a long list of domestic applications (e.g., '932, '148, '708), however, the oath/declaration and disclosure fail to clearly set forth the relationships of these various applications to the instant application and other intervening applications upon which priority is desired.

Information Disclosure Statement

3. Applicants are reminded the listing of references in the

specification is not a proper information disclosure statement. 37 C.F.R. § 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and M.P.E.P. § 609 ¶ A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited or considered by the examiner on a form PTO-892 or PTO-1449, they have not been considered.

4. According to the file wrapper of the instant application, it appears that an IDS was submitted on 10 January, 2001. However, perusal of the application failed to identify any relevant papers related to the submission. Appropriate clarification is required.

35 U.S.C. § 112, Second Paragraph

5. Claims 1-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites a number of changes in a primate lentivirus gp120 such as the introduction of disulfide bonds, "filling a cavity" with another amino acid, introducing an amino acid at a "defined turn structure", and increasing the "interface between the gp120 domains" which are vague and indefinite. First, many of the regions referenced (including the "discontinuous conserved epitope") are not clearly set forth. For instance, which amino acids comprise a "cavity"? Which amino acids make up a "defined turn structure"? Where is the "interface between the gp120 domains" located? Applicants should clearly and unambiguously identify the precise regions being subjected to mutagenesis as supported by the disclosure (i.e., a cavity located between amino acids 210-220; an alpha helix located between amino acids 20-30; an interface region comprising amino acids A, B, C, D, and E). Due to the genotypic variability of the lentiviruses, a

reference isolate should also be included in the claim language so the gp120 regions of interest can clearly be identified (i.e., wherein said numbering scheme is based upon the prototypical isolate HIV-1_{HXBc2}). Absent appropriate amendment, the metes and bounds of the patent protection desired cannot be ascertained.

6. Claims 2 and 15 are vague and indefinite for referencing two conserved epitopes designated CD4BS, CD4i, or 2G12. It appears that applicants are referencing the epitopes within the CD4 binding site, epitopes induced upon CD4-gp120 binding, and an epitope recognized by Mab 2G12. The first two epitopes will vary depending upon the antibodies used to map them. The binding specificity of Mab 2G12 is not clearly set forth. Thus, those amino acids that are critical for antibody/antigen binding are not clearly set forth. The claims should clearly and unambiguously identify the precise epitope and amino acids encompassed by the claimed invention.

7. Claims 8-10 are vague and indefinite for referencing mutations introduced at a "defined turn structure". It is not readily manifest which amino acids comprise this particular structure. Applicants should clearly set forth the amino acids encompassed by any given structural feature.

35 U.S.C. § 112, First Paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-16 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are broadly directed toward primate lentiviral envelope glycoproteins potentially carrying multiple mutations throughout. Such mutations encompass the introduction of disulfide bonds, replacements within a "cavity" of gp120, replacements within a "defined turn structure", and replacements at an "interface between the gp120 domains". The purpose of these mutations is to maintain the overall tertiary configuration of the SU glycoprotein which presumably will lead to enhanced stability and immunogenicity.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows: 1) The disclosure fails to clearly set forth those structural regions of the surface envelope glycoprotein that are to be modified. For instance, regions for the introduction of disulfide bonds are claimed, the replacement of amino acids at a "cavity", "defined turn structure", and "interface between the gp120 domains" are also set forth in the claim language. However, the disclosure

fails to clearly set forth those precise regions within the gp120 that are to be mutated.

2) The disclosure fails to identify those amino acids comprising a "discontinuous conserved epitope" of the wild-type gp120. In order to assess the effects of mutations on protein structure, the epitope influenced by such changes needs to clearly be identified. However, the disclosure fails to clearly identify the amino acids that are modulating any given antigen-antibody binding reaction.

3) The prior art teaches that amino acid replacements can affect the properties of the envelope glycoprotein in an unpredictable manner (Freed *et al.*, 1991; McKeating *et al.*, 1992; Thali *et al.*, 1993; Sullivan *et al.*, 1993; Cao *et al.*, 1993). Freed and colleagues (1991) performed single amino acid changes within the V3 loop and reported that "single amino acid changes in the V3 loop were capable of completely abolishing or greatly reducing the ability of the HIV-1 envelope glycoprotein to induce cell fusion". The authors noted that both conservative and non-conservative substitutions were capable of reducing syncytium formation significantly. McKeating *et al.* (1992) examined a different region of the HIV-1 Env and observed that single amino acid substitutions could greatly reduce or eliminate antibody binding. Thali *et al.* (1993) examined the affects of single amino acid substitutions on antibody binding to discontinuous epitopes and reported that "Single amino acid changes in five discontinuous, conserved, and generally hydrophobic regions of the gp120 glycoprotein resulted in decreased recognition and neutralization by the 17b and 48d antibodies." Thus, the skilled artisan can not predict *a priori*, how any given amino acid substitution will affect the immunological and biochemical properties of the protein.

4) The claims are of considerable breadth and encompass a large genus of poorly defined envelope molecules that are not clearly described and supported in the disclosure.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Correspondence

10. The Art Unit location of your application in the Patent and Trademark Office has changed. To facilitate the correlation of related papers and documents for this application, all future correspondence should be directed to **art unit 1648.**

11. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

12. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (703) 308-1122 or (703) 308-4027, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

10 July, 2003

PTO 892 DEA/FCE 1994 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE NOTICE OF REFERENCES CITED	SERIAL NUMBER 09/446,820	Art Unit 1648	Attachment to Paper Number 13
	APPLICANTS : Sodroski, J. G., *et al.*		

U.S. PATENT DOCUMENTS

*		DOCUMENT NUMBER	DATE	NAME(S)	CLASS	SUBCLASS	FILING DATE

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS		

*		OTHER REFERENCES (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)
		Freed, E. O., *et al.*, 1991, "Identification of the principle neutralizing determinant of human immunodeficiency virus type 1 as a fusion domain.", J. Virol. 65(1):190-194.
		McKeating, J. A., *et al.*, 1992, "Amino acid residues of the human immunodeficiency virus type 1 gp120 critical for the binding of rat and human neutralizing antibodies that block the gp120-sCD4 interaction.", Virol. 190:134-142.
		Thali, M., *et al.*, 1993, "Characterization of conserved human immunodeficiency virus type 1 and gp120 neutralization epitopes exposed upon gp120-CD4 binding.", J. Virol. 67(7):3978-3988.
		Sullivan, N., *et al.*, 1993, "Effect of amino acid changes in the V1/V2 region of the human immunodeficiency virus type 1 gp120 glycoprotein on subunit association, syncytium formation, and recognition by a neutralizing antibody.", J. Virol. 67(6):3674-3679.
		Cao, J., *et al.*, 1993, "Effects of amino acid changes in the extracellular domain of the human immunodeficiency virus type 1 gp41 envelope glycoprotein.", J. Virol. 67(5):2747-2755.

EXAMINER	DATE	* A COPY OF THIS REFERENCE IS NOT BEING FURNISHED WITH THIS OFFICE ACTION. (SEE MPEP SECTION 707.05(a).
Jeffrey S. Parkin, Ph.D.	07/10/03	PAGE 1 OF 1

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Mailing Date: December 26, 2000 Attorney/Sec: DSR/LAS/cll
Client: Dana-Farber Cancer Institute Docket No.: 700157-48436
Inventors: Sodroski et al.
Serial No.: 09/446,820 Patent No.:
Filing Date: November 10, 1998 Grant Date:

The dating stamp of the Patent and Trademark Office hereon will be taken as the date of filing of:

1. Certificate of Mailing (1 pg)
2. Information Disclosure Statement (3 pgs)
3. Form PTO 1449 (6 pgs)
4. References AA, CA-GX (129 Refs.)

Due Date: